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EXAMINER	
MARKS, M	
ART UNIT	**PAPER NUMBER**
105	7

DATE MAILED: 05/24/89

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3/2/89 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 14-38 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-13 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 14-38 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).
10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____; has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Examiner acknowledges applicants' election of Group II, claims 14-38 without traverse in Paper No. 6.

Claims 14-38 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to DNA constructs for expression of a chimeric polypeptide which is a subunit of an immunoglobulin molecule. See MPEP 706.03(n) and 706.03(z). This rejection is maintained for essentially the same reasons set forth in the previous office action.

Subunits of other multi-unit receptors which contain a variable region and constant region were not enabled (eg. T-cell receptors and Major Histocompatibility Complex antigens). Applicants' response of Paper No. 6 states that T cell receptors and Major Histocompatibility Antigens (MHC) are of the same supergene family as that of immunoglobulins, containing variable and constant regions, and are therefore enabled by the scope of their disclosure. Examiner disagrees with applicants argument that T cell receptors and MHC antigens were enabled in their disclosure because they contain variable and constant regions. The instant specification cites the receptors of interest "include B cell and T cell receptors, more particularly, Immunoglobulins (page 31 lines 23-25) yet does not provide a means for isolating the DNA encoding B and T cell receptors. Not all B and T cell receptors have variable and constant regions (eg CD2, CD7, CD20 and Fc). Cloning and sequencing of MHC antigens

was not disclosed or enabled in the instant specification. There are three major reasons why T cell receptors and MHC antigens are not considered within the scope of this invention. First, the instant specification does not disclose that these "multi-chain" receptors contain variable and constant regions and fails to describe how the DNA encoding such molecules would be isolated. It is well known to the immunogenetics art that isolating these latter proteins and their DNA was difficult. Second, not all T cell receptors have constant and variable regions. Only T cell receptors specific for antigens are composed of variable and constant regions, of which the variable region proteins were known to be homologous to immunoglobulins at the time of filing this application; but, again, this was not disclosed in the instant specification. However, at the time the instant specification was filed, it was not known that MHC antigens contained variable and constant regions. Third, it would require undo experimentation to isolate variable and constant region genomic sequence of these receptors for use in cross- species chimeric constructions.

Claims 14, 28, 33, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14, 28 and 36 are indefinite by claiming constructs

for a multi-unit receptor, cells, and a method for expressing a multi-unit receptor. Not all multi-unit receptors are taught in the instant invention. Is immunoglobulin intended rather than the genus multi-unit receptor? If DNA constructs encoding the supergene family of immunoglobulins, T-cell receptors and MHC antigens was intended, it should be named as such. The instant specification does not enable isolation of the DNA for both the constant and variable region genes encoding T cell receptors or MHC antigens.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless-

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14-34 and 36 are rejected under 35 U.S.C. 102(b) or 102 (e) as being clearly anticipated by Cabilly (L) or Cabilly (R) or Cabilly (2A).

This rejection is a new rejection which is essentially the same rejection set forth in the previous office action in the rejection of claims 14-34 and 36 over Cabilly (L).

Each of the Cabilly references cited above teaches various DNA constructs for the expression of chimeric immunoglobulin heavy chains, chimeric immunoglobulin light chains, chimeric immunoglobulins, and chimeric immunoglobulin fragments (ie.

chimeric subunits of a multiunit receptor). Cabilly teaches various expression vectors for use in either prokaryotic or eukaryotic host cells (See page 15 lines 6-29). Cabilly also teaches the use of eukaryotic host cells, including various mammalian cell types (page 18 line 6-34 and page 19 lines 1-8). Further, Cabilly teaches the use of the regulatory elements required for expression in vertebrate cells (page 18, lines 11-14). Finally Cabilly teaches the coexpression of both the heavy and light chains of immunoglobulin in the same host (page 23 line 29-30). Thus, all aspects of the instant invention, except for expression specifically in murine myeloma cells, was taught by Cabilly.

Note Cabilly (2A) in teaching the production of an immunoglobulin molecule. Note column 24 lines 60-66 and Figure 8C showing that cells double transformed with the construct for each immunoglobulin chain express both heavy and light chain proteins. Column 25 lines 45-68 and column 26 describe the reconstitution of antibody from recombinant heavy and light chains. The table in column 27 shows that the heavy and light chains were reconstituted to form functional immunoglobulins which specifically recognize antigen. 0.76% and 0.33% of the recombinant antibody chains were reconstituted as compared to 0.4% of the hybridoma produced antibody chains. Thus, Cabilly produced a functional chimeric antibody composed of recombinant

heavy and light chains. Further, Cabilly (R) teaches the motivation to express pre-light chains and pre-heavy chains in mammalian cells (page 3277 left paragraph) so that the immunoglobulin chains will be secreted and assembled in vivo.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office Action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 35 and 37-38 are rejected under 35 U.S.C. 103 as being unpatentable over Cabilly (L) or Cabilly (R) or Cabilly (2A) in view of Gillies (S).

Cabilly teaches the use of eukaryotic host cells , including vertebrate cell hosts (eg L, pages 18 and 19). In the absence of unexpected results, it would be obvious to use myeloma cells as a type of mammalian cell as taught by Cabilly. It would be particularly obvious to use myeloma cells to express a DNA

construct whose major regulatory and coding sequences are endogenous to said myeloma cell, since the endogenous host would contain the both 1) the trans-acting factors necessary for activating immunoglobulin cis elements and 2) the cytoplasmic organelles and enzymes required for co- and post-translational processing of immunoglobulin chains. Further, Cabilly (R) teaches the motivation to express pre-light chains and pre-heavy chains in mammalian cells (page 3277 left paragraph) so that the immunoglobulin chains will be secreted and assembled in vivo. Thus, one of ordinary sill in the art would be motivated to use mammalian cells to secrete immunoglobulin chains which are assembled in vivo. In the absence of unexpected results, one of ordinary skill in the art would be further motivated to use myeloma cells because of their properties discussed above which would be advantageous for expressing immunoglobulins.

Gillies teaches the use of mammalian cells, particularly myeloma cells, as well as the method for expressing immunoglobulin genes in myeloma cells. Applicants note on Paper No. 6 , page 6 that the two of the coinventors of the Gillies patent are co-inventors of the subject application. Therefore, examiner asserts that applicant would be motivated to use these known cells for their known properties. In the absence of unexpected results, it would be obvious to one of ordinary skill in the art to utilize the vector and cells of Gillies to express

the chimeric constructs of Cabilly in order to produce the chimeric receptor (ie. antibody or immunoglobulin fragment) of Cabilly.

Claims 28-35 are, rejected under 35 U.S.C. 103 as being unpatentable over Boss (2B) in view of Gillies (S).

Boss teaches the method of producing antibodies comprising transforming a host cell with DNA sequence encoding each of a heavy and light chain of an immunoglobulin. Gillies is applied as above in teaching the use of myeloma cells for expressing heterologous products and the particular advantages of myeloma cells in expressing immunoglobulin genes. ONe of ordinary skill in the art would be motivated to use the best host cell system for expressing a desired product. It would be particularly obvious to use the myeloma host cells of Gillies to express a DNA construct whose major regulatory and coding sequences are endogenous to said myeloma cell, since the endogenous host would contain the both 1) the trans-acting factors necessary for activating immunoglobulin cis elements and 2) the cytoplasmic organelles and enzymes required for co- and post-translational processing of immunoglobulin chains. In the absence of unexpected results, it would be obvious to one of ordinary skill in the art to use myeloma cells as host for expressing DNA constructs containing the transcriptional and translational regulatory elements which this cell recognizes specifically.

Any inquiry concerning this communication should be directed to Examiner Michelle Marks, Ph.D. at telephone number 703-557-0664.

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